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# A linear sesterterpene, two squalene derivatives and two peptide derivatives from *Croton hieronymi*

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Dedicated to the memory of Professor Jeffrey B. Harborne

**Abstract**

Aerial parts of *Croton hieronymi* furnished in addition to a large number of plant sterols and triterpenes the C-25 analog of *trans*-phytol, the squalene derivatives all-*trans*-2,6,15,19,23-pentamethyltetracosa-2,6,10,(28),14,22,28-hexaene-11-ol and all-*trans*-10-methylene-2,6,10,14,18,22-pentamethyltetracosa-1,6,10,14,18,22-hexaen-3-ol, the sesquiterpenes epicubenol and T-cadinol, the acetophenone derivative xanthoxylin and the peptide derivatives aurentiamide acetate and *N*-benzoylphenylalanyl-*N*-benzoylphenylalaninate.


*Keywords:* *Croton hieronymi*; Euphorbiaceae; Squalene derivatives; C-25 analog of *trans*-phytol; *N*-benzoylphenylalaninol peptides

## 1. Introduction

Numerous studies have dealt with the constituents of *Croton* species (Euphorbiaceae, Crotonoideae) more than 700 representatives of which are found in warm and tropical regions. Diterpenoids of various types are particularly well represented (Lalou et al., 1999; Kapingu et al., 2000; Roengsumran et al., 2001; Sutthivaiyakil et al., 2001; Vigor et al., 2001; Block et al., 2002) and alkaloids are also common (Amaral and Barnes, 1998). As a MeOH extract of the aerial parts of *Croton hieronymi* Griseb., a native of northwestern Argentina, showed strong activity against lung carcinoma cells A-549 ($IC_{50} = 0.25$ μg/ml) and mouse lymphoma ($IC_{50} = 1$ μg/ml) and some activity against human colon carcinoma ($IC_{50} = 2.5$ μg/ml), we have undertaken a study of its constituents. The chemical composition and antimicrobial activity of the leaf and root essential oils of this plant have been described elsewhere (de Heluani et al., in press). In the following we describe our work on the chloroform extract of the aerial parts of *C. hieronymi*, affording **1–10** among other compounds.

## 2. Results and discussion

HPLC coupled with $^{13}C$ NMR spectral analysis and in a number of instances with GC–MS, led to identification in the extract of a large number of triterpenes and plant sterols, i.e. α- and β-amyrin, lupeol, hop-22(29)-en-β-3-ol, cholesterol, cholest-8(14)-en-3β-ol, stigmasterol, gramisterol, sitosterol, campesterol, 22-dihydrobrassicasterol, lophenol, isofucosterol stigmasterol, cholest-4-en-3-one, ergosta-4,22-dien-3-one and sitostenone. Known sesquiterpenoids were epicubenol (**7**, Ohta and Hirose, 1967) and T-cadinol (**8**, Claeson et al., 1991). Relatively large amounts of xanthoxylin (**6**) were also found.

The squalene derivative **1** is new as a natural product but has been previously synthesized, although not thoroughly characterized, by reaction of squalene 10,11-epoxide, isolated from the marine green alga *Caulerpa prolifera*, with aluminum isopropoxide in boiling toluene (de Napoli et al., 1982). The $^1H$ NMR spectrum exhibited

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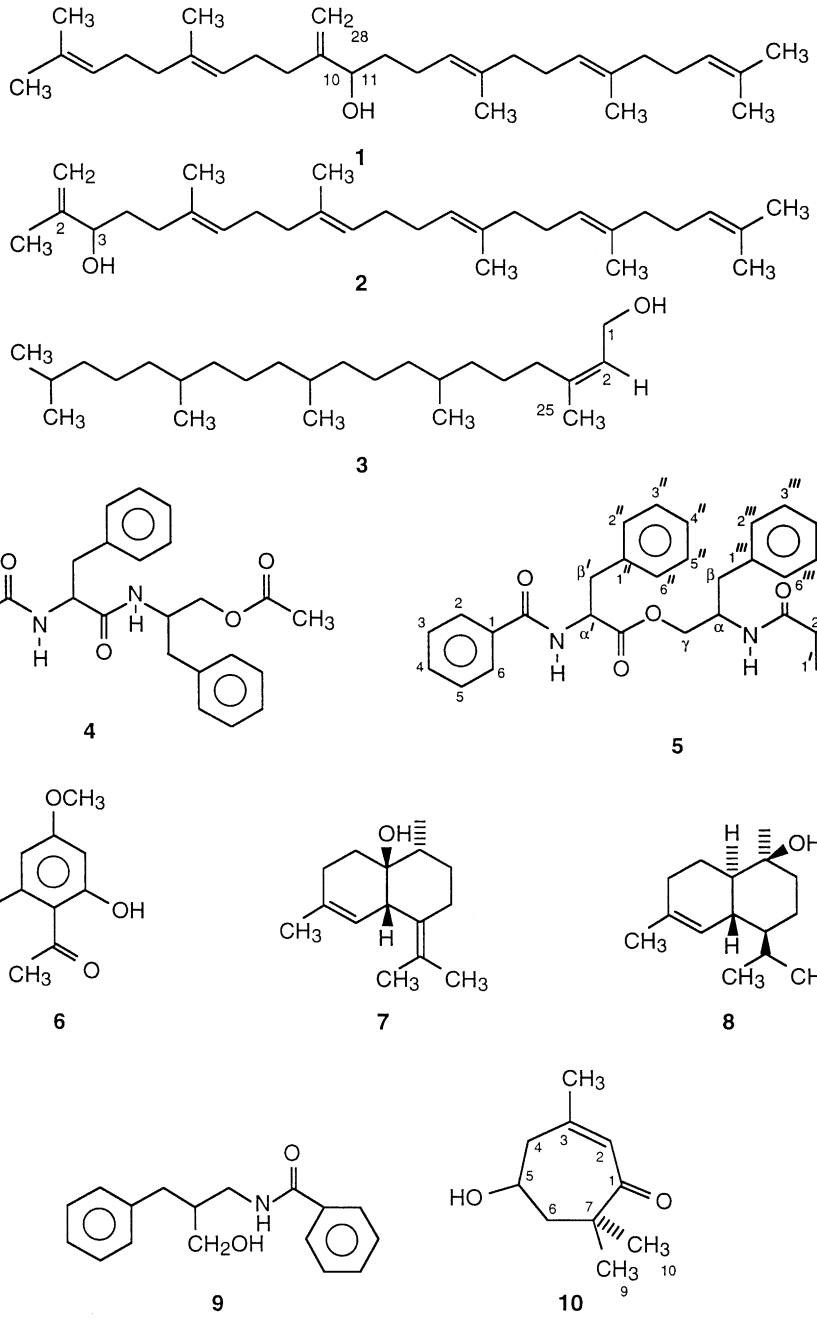

signals of five vinylic protons at $\delta$ 5.12 (*m*, 2p) and 5.08 (*tquint* or *tsept*, $J=7$, 1.5 Hz, 3p, H-3,7,14,18,22), two further vinylic protons at $\delta$ 5.02 (*brs*) and $\delta$ 4.85 (*q*, $J=1.5$ Hz, H-28a,b), a *brddd* at $\delta$ 4.05 ($J=12$, 7, 5 Hz, H-11 coupled to H-12a,b, H-9b and H-28 a,b) and six vinylic methyls, the location of the methylene double bond being established by double irradiation experiments involving H-28a,b which affected only the hydrogens under the hydroxyl and one adjacent methylene which was not on C-5. Squalene derivative **2** was identical with a squalene derivative isolated by de Napoli et al. (1982) from the same alga as shown by the HRMS and the $^1$H NMR spectrum which exhibited signals at $\delta$ 5.11 (*brquint*, $J=7$, 1.5 Hz, 2p) and 5.07 (*tquint*, $J=7$, 1.5 Hz, 3p, H-7, 11, 14, 18, 22), 4.92 (*quint*, $J=1$ Hz) and 4.82 (*quint*, $J=1.5$ Hz, H-1,a,b), 4.02 (*brdd*, $J=7$, 5.5 Hz, H-3), 2.05 *m* and 1.98 *m* (18 p), 1.71 (*brs*, 3 p, 2-Me), 1.66 (*brs*, 3p, H-24), 1.60 (*m*, 2p, H-4a,b), 1.60 (*brs*, 3p, H-25), 1.59 (*brs*, 12H, H-26-29).

A new sesterterpene was the $C_{25}$ analog **3** of *trans*-phytol, based on the $^1$H NMR spectrum which exhibited five methyl doublets including those of C-20 and C-21 coupled to H-19 represented by a multiplet at $\delta$ 1.50, the signal of H-2 at $\delta$ 5.39 vicinally coupled to the two protons on C-1

at $\delta$ 4,13 ($d$, $J = 7$) and allylically to the protons on C-4 and the vinyl methyl (C-25). Occurrence of this substance in the volatile lipids of *Methanobacterium* species has been surmised based on mass spectrometric evidence following silylation (Risatti et al., 1984).

A surprising constituent was the peptide derivative aurentiamide acetate (**4**) previously found in an *Aspergillus* species (Cox et al., 1976), two algae (Maiti and Thomson, 1976; Wahidulla et al., 1991) and several higher plants (Banerji and Das, 1975; Uemura et al., 1975; Banerji and Ray, 1981; Poi and Adityachaudhury, 1986; Anjaneyulu and Raju, 1988; Tsai et al., 1998) and named saropeptide by Ishiguro et al. (1991) without reference to earlier work. The only other member of Euphorbiaceae listed as a source of **4** is *Euphorbia fischeriana* (Uemura et al., 1975). A new peptide derivative was *N*-benzoylphenylalaninyl-*N*-benzoylphenylalaninate (**5**) which differed from **4** in that the left half of **4** was esterified by N-benzoylphenylalaninol as shown by the chemical shifts of H$\alpha'$, H$\beta'$ and H$\gamma'$ and the presence of a second benzamide functionality. Extensive decoupling of the $^1$H NMR spectrum and the $^{13}$C NMR spectrum, both listed in the Experimental section, and the HRMS established the assigned structure. *N*-Benzoylphenylalaninol itself (**9**) turned up as a minor constituent of one of the most polar fractions. Compounds of this type are rare and have not previously been found in *Croton* species.

## 3. Experimental

### 3.1. General

HPLC operations utilized a Phenomenex LUNA column (5 μ,10 ×250 mm) equipped with a differential refractive index detector with retention times being measured from the solvent peak. GC–MS analyses were carried out on a GC-HP 6890 with a quadrupole mass selective detector HP5973, source 70 eV, fitted with a HP-5MS column (5% phenylmethylsiloxane, 30 m×0.25 μm) using helium as carrier gas (1.0 ml/min$^{-1}$). $^1$H NMR spectra were obtained on a Varian Inova 500 MHz NMR spectrometer in $CDCl_3$, whereas $^{13}$C NMR spectra were run on an IBM/Bruker WP270SY NMR spectrometer at 67.5 MHz in $CDCl_3$. Mass spectra were acquired on a Jeol MS Route 600 H instrument. Melting points were taken on a Fisher-Jones apparatus and are uncorrected. Si gel chromatography was Si gel 60 (0.2–0.5 mm) Merck. Known compounds were identified by $^1$H NMR and MS and comparison with literature data.

### 3.2. Plant material

Aerial parts of *Croton hieronymi* were collected in December 1997 at Cuenca Tapia, Trancas Department, Tucumán Province, Argentina. A voucher specimen (LIL N° 604.138) is on deposit in the herbarium of Instituto Miguel Lillo, Tucumán, Argentina.

### 3.3. Extraction and isolation

Aerial parts (458 g) of *C. hieronymi* were extracted with $CHCl_3$ (2 × 3 l) at rt for 3 days. Evaporation of the extract in vacuo gave crude extract (10.51 g, 2.3% yield) which was suspended in MeOH (180 ml) at 60 °C, diluted with water (20 ml) and extracted successively with hexane (3 × 40 ml) and $CHCl_3$ (2 × 50 ml). Evaporation of the hexane extract gave a residue (2.75 g) which was subjected to cc over Si gel (230–400 Mesh) using hexane and increasing amounts of EtOAc (0–15%) to give 359 fractions which were selectively combined on the basis of their profiles on TLC. Fractions 70–83 (60 mg) were processed by HPLC (MeOH–$H_2O$, 97:3; 2 ml min$^{-1}$) to give epicubenol (**7**) (6.3 mg, $R_t$ 4.0 min, mp 28.5–29.5°) (Ohta and Hirose, 1967), and **1** (2.4 mg, $R_t$ 29.0 min). Frs 84–93 (45 mg) were subjected to HPLC in the same manner and gave 9 mg of **6** ($R_t$ 1.5 min), T-cadinol (**8**, 3.1 mg, $R_t$ 5.0 min) (Claeson et al., 1991), **2** (1.1 mg, $R_t$ 30.0 min). HPLC (MeOH–$H_2O$, 9:1; 2 ml min$^{-1}$) of frs 94–105 (83 mg) gave an additional 8 mg of **6** ($R_t$ 2.5 min), and 12.0 mg of **8**; mp 48.0–50.0°). Frs 106–120 which had an $R_f$ close to β-amyrin were combined and subjected to HPLC (MeOH, 2 ml min$^{-1}$), the peaks were collected separately, and the residues analyzed by GC–MS. The following compounds were identified in this manner: lupeol (3 mg), cholest-4-ene-3-one (5 mg), hop-22(29)en-3β-ol (moretenol, 1.2 mg), ergosta-4,22-dien-3-one (0.6 mg), β-amyrin (3.3 mg), α-amyrin (10.0 mg) and stigmast-4-en-3-one (6.3 mg). Stirring of fractions 121–142 (168 mg) in MeOH afforded 31.8 mg of a mixture of dihydroxymethoxyacetoxyacetophenones ($^1$H NMR analysis) as a solid, mp 76–78.0°; the MeOH solubler was subjected to HPLC (MeOH–$H_2O$, 2 ml min$^{-1}$) to give a complex mixture (23.4 mg, $R_t$ 10.0 min), phytol (4.4 mg) and additional amounts of lupeol (2.9 mg), β-amyrin (11.8 mg), α-amyrin (13.5 mg) and stigmast-4-en-3-one (1.0 mg), which were identified by GC–MS. Frs 143–172 (98 mg) on HPLC (MeOH–$H_2O$, 2 ml min$^{-1}$) gave **3** (3.2 mg, $R_t$ 9 min), β-sitostenone (1.1 mg) and gramisterol (2.1 mg), both identified by $^1$H NMR and MS, a mixture (1 mg) of eicosanol, lophenol, cholest-8(14)-en-3-β-ol and β-amyrin, whose constituents were identified by GC–MS, and α-amyrin (0.6 mg). HPLC of frs 190–220 (238 mg) (MeOH–$H_2O$, 2 ml min$^{-1}$), the eluate being analyzed by GC–MS, afforded sitosterol (34 mg) also identified by $^1$H NMR spectrometry and MS, 19:1 (2.4 mg) mixture of cholesterol and isofucosterol, stigmasterol (1.0 mg) and a 3:1 mixture (7.2 mg) of campesterol and stigmasterol. Frs 229–281 (180 mg) were decolorized by flash CC on florisil; HPLC of 20 mg (MeOH–$H_2O$, 95:5; 2 ml min$^{-1}$) gave

only mixtures of long chain acids as shown by $^1$NMR and MS.

The $CHCl_3$ extract (1.11 g) was subjected to chromatography over Si gel (230–400 Mesh) using $CHCl_3$ and increasing amounts of EtOAc (0–25%) to give 140 fractions which were combined on the basis of their TLC profiles. Frs 4–5 (54 mg) on HPLC (MeOH–$H_2O$, 2 ml min$^{-1}$) gave xanthoxylin (**6**, 20.9 mg, $R_t$ 3.0 min$^{-1}$) (Cunningham et al., 1989). Frs 10–15 (59 mg) on HPLC gave triterpene mixtures which were not further characterized. Frs 30–43 (50 mg) were stirred in 2 ml MeOH; the resulting solution on HPLC (MeOH–$H_2O$, 4:1; 2 ml min$^{-1}$) gave 4.2 mg of **5** ($R_t$ 14.0 min). Stirring of frs 44–59 (32 mg) with 11 ml of MeOH–$H_2O$, (9:1) resulted in formation of 3.8 mg of solid **5**. The MeOH solubles on HPLC (MeOH–$H_2O$, 9:1; 2 ml min$^{-1}$) gave 7.4 mg of **4** ($R_t$ 2.5 min), 8.5 mg of **5**, ($R_t$ 4.0 min) and 4.2 mg of a mixture of long chain acids as shown by $^1$H NMR and MS ($R_t$ 45 min, mp: 62.5–63.0°). Stirring of frs 60–100 (75 mg) in MeOH–$H_2O$ (4:1) caused separation of unidentified solids (3.5 mg); HPLC of the supernatant (MeOH–$H_2O$, 81.3:18.7; 2 ml min$^{-1}$) gave 6.5 mg of **4** ($R_t$ 6.0 min). Flash chromatography over Si gel (230–400 mesh) of frs 101–112 (26 mg) using $CHCl_3$–EtOAc (19:1) gave 11.5 mg of a mixture the constituents of which were not further separated. Analysis of the mixture by $^1$H NMR spectroscopy indicated that a minor constituent was the right-hand component of substance **5**, i.e. the previously unknown benzoylphenylalaninol (**9**) which exhibited signals ($CDCl_3$) at $\delta$ 7.65 (2p, *dd*, $J$=8,1.5 Hz, H-2,6 of benzamide), 7.47 (1p, *tt*, $J$=8,1.5 Hz, H-4 of benzamide), 7.39 (2p, *td*, $J$=8,1.5 Hz, H-3,5 of benzamide, 7.31 (2p, *td*, $J$=8,1.5 Hz, H-3,5 of phenyl), 7.21 (2p, *dd*, $J$=8,1.5 Hz, H-2,6 of phenyl), 7.23 (1p, *tt*, $J$=8,1.5 Hz, H-4 of phenyl), 4.35 (1p, *dddd*, $J$=5, 3.5, 2.5, 2.5 Hz, H α to amide NH), 3.78 and 3.70 (1p each, *dd*'s, $J$=11, 3.5 and 11, 5 Hz, $CH_2OH$), 3.00 and 2.97 (1p each, $J$'s=12, 2.5 Hz, benzylic protons). A larger fraction of the mixture consisted of a polar monoterpene, apparently the new eucarvone derivative **10** whose $^1$H NMR spectrum (assignments by spin decoupling), exhibited signals at $\delta$ 5.69 (*s*, H-2), 4.11 (*tt*, $J$'s=12, 12, 4, 4, Hz, H-5), 2.51 (*ddd*, $J$=12, 4, 2.5 Hz), 2.01 (*ddd*, $J$=12.5, 4, 2.5 Hz), 1.48 (*t*, $J$=12 Hz) and 1.31 (*t*, $J$=12 Hz (H-4a,b, H-6a,b), 1.56 (*s*, 3p, H-8), 1.29 and 1.24 (both *s* and 3p, H-9 and H-10).

### 3.4. All-trans-2,6,15,19,23-pentamethyltetracosa-2,6,10(28),14,22,28-hexaene-11-ol (1)

Gum; HRMS+FAB (Na) 449.3739; $C_{30}H_{50}O$+Na requires 449.3759; $^1$H NMR spectrum $\delta$ 5.12 (*m*, 2p) and 5.08 (*tquint* or *sept*, $J$=7, 1.5 Hz, H-3, 7, 14, 18, 22); 5.02 (*brs*) and 4.85 (*q*, 1.5 Hz, H-28a,b), 4.05 (*ddd*, $J$=12, 7, 5 Hz, H-11), 2.14 (*brs* or *sept*, 7 Hz, 1p), 2.04 (*sept*, 7 Hz, 8p), 1.97 (*quint*, 7 Hz, 6p), 1.66 (*brs*, 6p, 2 Me), 1.61 (*brs*, 6p, 2 Me), 1.58 (*brs*, 9p, 3 Me).

### 3.5. All-trans-10-methylene-2,6, 10, 14,18,22-pentamethyl-tetracosa-1,6,10,14,18,22,-hexaen-3-ol (2)

Gum; HRMS+FAB (Na) 449.3753; $C_{30}H_{50}O$+Na requires 449.3759; $^1$H NMR spectrum $\delta$ 5.11 (*brquint*, 7, 1.5 Hz) and 5.07 (*tquint*, $J$=7, 1.5 Hz, 5p), H-7, 11, 14, 18, 22), 4.92 (*quint*, $J$=1 Hz) and 4.82 (*quint*, $J$=1.5 Hz, H-1a,b), 4.02 (*brd*, $J$=7, 5.5 Hz, H-3), 2.05 (*m*) and 198 (*m*,18p, H-5, H-8<H-9, H-11, H-12, H-14, H-15, H-17, H-18), 1.71 (*brs*, 3p, 2 Me), 1.66 (*brs*, 3p, H-24), 1.60 (*m*, 2p, H-4a,b), 1.60 (*brs*, 3p, H-25), 1.59 (*brs*, 12 H, H-26-29).

### 3.6. 2E-3,7,11,15,19-Pentamethyleicos-2-1-ol (3)

Gum; MS PCI 367 (M+H, 100), 349 (65); $C_{25}H_{50}O$+H requires 366. The substance had undergone partial decomposition by the time HRMS could be run; $^1$H NMR ($CDCl_3$) $\delta$ 5.39 (*tq*, $J$=17, 1.5 Hz, H-2), 4.14 (2p, *d*, $J$=7 Hz, H-1,a,b), 1.97 (2p, *brt*, $J$=7 Hz, H-4a,b), 1.65 (*brs*, 3p, H-25), 1.50 (1p, *nonet*, $J$=7 Hz, H-19), 0.845 (*d*, $J$=7 Hz, 9p), 0.833 (*d*, $J$=7 Hz, 3p), 0.829 (*d*, $J$=7 Hz, 3p); $^{13}$C NMR ($CDCl_3$) $\delta$ 140.35 *s* (C-3), 123.06 *d* (C-2), 59.44 *t* (C-1), 39.86 and 39.36 (three *t*, superimposed signals), 37.42 *t* (two superimposed signals), 37.28 *t* (three superimposed signals), 36.62 *t*, 32.74 *d* (two superimposed signals) and 32.64 *d* (C-7, 11, 15), 27.93 *d* (C-19), 25.09 *t*, 24.74 *t* (two superimposed signals), 24.25 *t*, 22.66 *q* (two Me), 25.79 *q*.

### 3.7. Aurentiamide acetate (N-benzoylphenylalaninoyl-phenlyalaninolacetate (4)

Mp 182–183.5°, lit. 184°, HRMS+FAB (Na) 467.1975, $C_{27}H_{28}O_4N_2$+Na requires 467.1947; $^1$H and $^{13}$C NMR spectra as reported by Ishiguro et al. (1991).

### 3.8. N-Benzoylphenylalaninyl-N-benzoylphenylalaninate (5)

Mp 212.5–213°, HRMS+FAB (Na) 529.2122, $C_{32}H_{30}O_4N_2$+Na requires 529.2103; $^1$H NMR ($CDCl_3$) 4.90 (*q*, $J$=H-7 Hz, H-α′), 3.27 (*dd*, $J$=14, 6.5 Hz, H-$\beta'_a$), 3.19 (*dd*, $J$=14, 7 Hz, H-$\beta_b$), 4.60 (*dddd*, $J$=8, 6.5, 4, 3.5 Hz, H-α′), 2.98 (*dd*, $J$=14, 6.5 Hz, H- $\beta'_a$), 2.87 (*dd*, $J$=14, 8 Hz, H-$\beta'_b$), 4.52 (*dd*, $J$=11, 3.5 Hz, H-$\gamma_a$), 4.02 (*dd*, $J$=11, 4 Hz, H-$\gamma_b$), 7.68, (2p, *dd*, $J$=8, 1.5 Hz, H-2,6), 7.30 (2p, *td*, $J$=8, 1.5 Hz, H-3,5), 7.41 (*tt*, $J$=8, 1.5 Hz, H-4), 7.64 (2p, *dd*, $J$=8, 1.5 Hz, H-2, 6,) 7.37 (2p, *td*, 8, 1.5 Hz, H-3, 5), 7.48 (*tt*, $J$=8, 1.5 Hz, H-4′), 7.27c and 7.20c (10p, aromatic protons on phenyl rings), 6.61 (*brd*, $J$=8.5 Hz, $NH_b$-), 6.53 (*brd*, $J$=6 Hz, $NH_a$), 4.99 (*q*, $J$=7 Hz, Hα), 4.60 (*dddd*, $J$'s=8, 6.5, 4,

3.5 Hz, Hα′), 4.52 (*dd*, $J=11$, 3.5 Hz, H-$\gamma_\alpha$), 4.02 (*dd*, $J=11$, 4 Hz, H-$\gamma_b$), 3.27 (*dd*, $J=14$, 6.5 Hz, H-$\beta_a$), 3.19 (*dd*, $J=14$, 7 Hz, H-$\beta_b$), 2.98 (*dd*, $J=14$, 6.5 Hz, H-$\beta'_a$), 2.87 (*dd*, $J=14$, 8 Hz, H-$\beta'_b$); $^{13}$C NMR ($CDCl_3$) δ 171.91 (*s*, lactone C=0), 167.42 and 167.21 (both *s*, benzamide C=O's), 133.32 *s* (C-1), 134.20 (*s*, C-1′), 127.11 (*d*, C-2,6), 127.04 (*d*, C-2, 6), 128.61 (*d*, C-3,5), 128.69 (*d*, C-3,5), 132.02 (*d*, C-4), 131.39 (*d*, C-4), 137.74 and 135.14 (both *s*, C-1, C-1), 129.30 (*d*, two signals) and 129.16 (*d*, two signals, C-2, 6, C-2, 6), 128.72 (*d*, two signals) and 128.71 (*d*, two signals, C-3, 5, C-3, 5), 126.77 (*d*) and 127.17 (*d*, C-4, 4), 65.42 (*t*, C-γ), 54.47 (*d*, C-α), 50.28 (*d*, C-α′), 37.54 and 37.26 (both *t*, C-β and C-β′) 19.69 *q*, 16.129 (two Me).


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